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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,552	01/26/2006	Gerd Wallukat	3035-111	7096

46002 7590 04/14/2009

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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
04/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,552	WALLUKAT, GERD	
	Examiner	Art Unit	
	David A. Saunders	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,15-25 and 30-37* is/are pending in the application.

4a) Of the above claim(s) *16-25,30,31,33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15,32 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/27/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

AMENDMENT ENTRY

Amendment of 1/27/09 has been entered. Claims 1-12, 15-25 and 30-37 are pending. Claims 1-12, 32 and 35-37 are under examination. Claim 32 is being examined for the embodiment of "diagnosis or monitoring". It is considered that this embodiment involves “providing” a “Peptide selected from the group consisting of” the peptides listed in part “a)”.

Since the claims are not in condition for allowance, the elected species remain as the peptide of SEQ ID NO:3 and the disease(s) recited as dilatative cardiomyopathy/ myocardiopathy. However, the Office shall consider other species, to the extent that they may be disclosed in any pertinent references in the IDS filed 1/27/09.

OBJECTION(S)/REJECTION(S) OF RECORD WITHDRAWN

The amendment has overcome previously stated issues as follows:

The objection to the Drawings.

The objection to the specification.

The objection to claim(s) 8 under 37 CFR 1.75.

The objection to claims 12, 32 and 35 for failure to recite SEQ ID NOS.

The rejection of claim(s) 6, 9 and 11-14 under 35 USC 112, 2nd paragraph.

The rejection of claim(s) 1-15 under 35 USC 112, 1st paragraph regarding the use of a denaturing agent.

The rejection of claim(s) 1-15 under 35 USC 112, 1st paragraph regarding the use of a peptide lacking biotin or a tag.

The rejection of claim(s) 13-14 under 35 USC 112, 1st paragraph, since these claims have been cancelled.

The rejection of claim(s) 32 and 35 under 35 USC 101 for failing to recite a proper process claim.

The prior art rejection of claims 1-8, 10-13 and 15 under 35 U.S.C. 103(a) as being unpatentable over Wallukat et al, (J. Molec. Cell. Cardiol. 1995) and Ronspeck et al (WO 01/21660 or US 6,994,970), both in view of Aalberse (US 4,468,470). In addition to applicant's arguments, the Office notes that Aalberse teaches detection of antibodies in a serum sample, not in an ammonium sulfate fraction of the serum. Wallukat et al show enzyme immunoassay testing of autoantibodies prepared by an ammonium sulfate fractionation and by affinity chromatography. However, these immunoassays are merely used to titrate the purified autoantibodies that are used in functional studies of cultured cardiocytes; there is therefore no suggestion by Wallukat et al to purify the autoantibodies, prior to detecting the autoantibodies for the purpose of diagnosis.

The prior art rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Wallukat et al, and Ronspeck et al, both in view of Aalberse, as applied to claim 1, and further in view of Staudt et al (Circulation, 106, 2448, 2002). Since the rejection of claim 1 has been withdrawn, the rejection of dependent claim 9 is likewise withdrawn.

NEW OBJECTION(S) TO CLAIMS

Claims 9, 11 and 32 are objected to because of the following informalities:

In claim 9, line 8 "is detected" should be –are detected--.

In claim 11, line 7 "bind" should be –binds--.

In claim 32, line 1, --or-- needs to be inserted after "diagnosis".

Appropriate correction is required.

Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 fails to further limit base claim 1, because step a) of claim 1 serves to concentrate and/or purify the autoantibodies.

REJECTION(S) UNDER 35 USC 112, SECOND PARAGRAPH

Claims 1-15, 32 and 35-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is newly rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: between steps a and b) applicant has disclosed the essential step in which the separated components [i.e. the precipitated autoantibodies] can be returned to essentially the native state that allows their detection." See spec. page 6, 2nd full para. Unless the precipitated autoantibodies are returned to their native state, these autoantibodies will not bind to the peptide that is added in step b).

Claim 10 remains indefinite for failing to state where, in the sequence of steps recited in base claim 1, the autoantibodies become "concentrated or purified". By virtue of the recitation of "before being detected", one does not know of the autoantibodies become "concentrated or purified" before step a) of claim 1,or if the autoantibodies become "concentrated or purified" before step f) of claim 1, in which one is "to detect disease-associated autoantibodies". In this regard, the examiner notes that the references of record (e.g. Wallukat et al, J. Molec. Cell. Cardiol. 1995, at p 399) indicate that the steps involved in affinity purification would be conducted after ammonium

sulfate precipitation (i.e. step a) of claim 1), and after the antibodies in the precipitated Ig fraction are returned to "essentially the native state that allows their detection" (see para. above). However, the examiner cannot determine if applicant can enter such a limitation into claim 1, without entering new matter.

Claims 32 and 35 have been amended such that they recite a first step of "providing" a peptide selected from a Markush group and then conclude with a method of "diagnosing" or "detecting". Since, in each case, the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. That is, no steps recite what one is supposed to do with any provided peptide. No steps indicate where any detected antibody comes from. The amended versions of claims 32 and 35 are thus incomplete, without any active, positive steps delimiting how the provided peptide is to actually be employed in the method to be practiced. Claims 32 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

For claim 35, the omitted step, at the least, is that of bringing a bodily fluid into contact with a provided peptide, whereby autoantibodies bind said peptide. This omitted step is required after the "providing" step.

Furthermore, the "detecting" step of claim 35 has no nexus to the rest of the claim. It is suggested that applicant recite this as: detecting said autoantibodies bound to said peptide.

Claim 32 is likewise incomplete. For the embodiment in which a peptide of part a) is provided (which is the only embodiment under consideration), claim 32 would need to be amended as suggested supra for claim 35. However, note that claim 32 is less complete than claim 35, because applicant has not introduced any "detecting" step in claim 32. Claim 32 would also require a step that relates the detection of autoantibodies to the diagnosis of or the progression of said autoimmune disease.

Note that the above suggested additions to claims 32 and 35 constitute the minimum that would need to be added. Depending upon what the written description

has stated as the minimum, applicant may need to add more steps, in order to avoid a new matter rejection.

MAINTAINED REJECTION(S) UNDER 35 USC 112, FIRST PARAGRAPH

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant was not in possession of the genus of peptides that have been "modified by means of a deletion, addition and/or substitution."

Since the substitution of a single amino acid within any given parent polypeptide sequence can abolish the binding of an antibody thereto (Lederman et al, Molec. Immunol. 28, 1171-1181, 1991, cited on PTO-892), the use of a peptide other than one having a naturally occurring sequence from "the first and/or second loop" would not likely provide a peptide which would serve as a cognate antigen for detecting disease associated autoantibodies. This position will be maintained irrespective of whether the modification is substitution, or alternatively, a deletion or an insertion. The only possible modification that one of skill could readily envision would be that one could add on flanking residues, such as residues which naturally occur, within the "the first and/or second loop", on one or both sides of an identified epitopic peptide sequence, or such as the residues of a fused tag/flag sequence, or such as a single Cys residue (e.g. for covalently coupling the peptide to a carrier) However, the examiner cannot determine whether applicant has described these kinds of additions. On the other hand, applicant has given the public no direction as to where, within any of the exemplified epitopic peptide sequences, modifications can be made, of any kind, that would permit the peptide to retain its capacity to serve as a cognate antigen for detecting disease associated autoantibodies. One of skill, given any one of the exemplified peptide sequences, thus would not be able to determine which peptides, having one or more modification(s) within their internal sequence, would be members of the genus of

useable peptides that would serve as cognate antigens for detecting disease associated autoantibodies.

Applicant's arguments filed 1/27/09 have been fully considered but they are not persuasive because they point to articles which show that one of skill could have made appropriate deletions, additions or substitutions. These articles have no probative value, because what one of skill could have or might have done is not at issue. What is at issue is a written description of the actual deletions, additions or substitutions that would be appropriate. The articles merely indicate that one could have screened for peptides having the appropriate deletions, additions or substitutions; but they do not provide a description of what these variant peptides actually would be. The written description requirement cannot be met by showing that the invention might have been enabled for one of skill, since written description and enablement are separate aspects of 35 USC 112. Lockwood v. American Airlines… 107 F.3d 1505, 41 USPQ2d 1961.

NEW REJECTION(S) UNDER 35 USC 112, FIRST PARAGRAPH

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. A step¸ between steps a and b) in claim 1, in which "the separated components [i.e. the precipitated autoantibodies] can be returned to essentially the native state that allows their detection." is critical or essential to the practice of the invention, but it has not been included in the claim(s). The claimed invention is thus not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

See spec. page 6, 2nd full para. for teachings in this regard. One of skill would expect that, unless the precipitated autoantibodies are returned to their native state, these autoantibodies will not bind to the peptide that is added in step b); since the antigen binding activity of an autoantibody, or any antibody, requires that an antibody's antigen binding site be essentially in its native configuration. Note that, in the preparation of any antibody by an ammonium sulfate precipitation, one conventionally

re-dissolves the precipitate (e.g. in PBS) and dialyzes it. See, for example, Harlow et al at p 299, particularly at step 8 and Note i, which both refer to "the antibody solution" (that is obtained after dialysis). Such a step in which the ammonium sulfate precipitate is re-dissolved is taken to correspond to a step, in which "the separated components can be returned to essentially the native state". Since this step of re-dissolving is conventional it is taken to be a method "known to a person skilled in the art", as recited by applicant at spec. page 6, 2nd full para. For this reason, the examiner considers that insertion, after step a) of a step, in which "the separated components can be returned to essentially the native state that allows their detection" would meet the requirements of 35 USC 112 with respect to both description and enablement.

Even it were granted that the precipitated antibody might possibly bind the peptide(s) added in step b), one of skill would still not know how to then conduct step c); that is to say, how would one get peptide-autoantibody complexes in a precipitate to get captured onto the carrier of step c)? Such a capturing step (e.g. via avidin-biotin binding) would require that the peptide-autoantibody complexes be in solution, rather than in a precipitate.

MAINTAINED REJECTION(S) UNDER 35 USC 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32 And 35 Are rejected under 35 U.S.C. 102(b) or (e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over either Wallukat et al, (J. Molec. Cell. Cardiol. 1995) or Ronspeck et al (WO 01/21660 or US 6,994,970).

The US and foreign references of Ronspeck et al have the same disclosure. For convenience the examiner will refer to the US document by col. and line number. Only the US document is supplied, since the instant applicant is a co-inventor with Ronespeck.

Wallukat et al teach the peptide sequences which constitute the dominant autoantibody-reactive epitopes of the first and second extracellular loops of the β1 adrenoreceptor (andrenegen receptor). These are identical to the peptides having instant SEQ ID NOS: 2 and 3. Wallukat et al note that earlier investigators have shown that the sera of DCM patients contains autoantibodies that react with peptides derived from the first and second extracellular loops of the β1 adrenoreceptor (p 398, col. 2).

Ronspeck et al teach the same epitopic sequences as Wallukat et al, except that Ronspeck et al provide these peptides with flanking sequences derived from the first or second extracellular loops of the β1 adrenoreceptor. Ronspeck et al conduct an ELISA assay for autoantibodies in the sera of DCM patients. See col. 8, lines 11-44. Therein Ronspeck et al refer to the teachings of Wallukat et al regarding assays. Neither the Wallukat et al nor Ronspeck et al references teach the precise method by which they conducted assays for autoantibodies in the sera of DCM pateints. However, the claims do not require any particular immunoassay format, and do not require the use of any particular reagent, except for one or more of the provided peptides. Since each of the references teaches the peptides, claims 32 and 35 are anticipated or, at the least, would have been obvious.

Applicant's arguments filed 1/27/09 have been fully considered but they are not persuasive because they point to amendments that have been made in, merely, the

preamble and the conclusion of the claims. Since nothing in the body of the claims states anything unobvious, given a disclosure of epitopic peptides that are recognized by autoantibodies and a teaching that one would want to detect such autoantibodies, the claims remain rejected over the prior art.

NEW REJECTION(S) UNDER 35 USC 102

Claims 1-5, 7-10, 15 and 37 are rejected under 35 U.S.C. 102(a) or (b) as being entirely anticipated by Wallukat et al (In vitro Cellular…, vol. 38, 376-377, Jul/Aug 2002, cited in IDS of 1/27/09).

The reference is alternatively cited under 102(a) or (b). The 102(b) rejection is based upon the fact that the date of Jul/Aug 2002 is 102 (b) is more than 1 year prior to 11/28/03 filing date of PCT/DE03/03988. To overcome the 102 (b) rejection, applicant must provide translation(s) of one or more of the 3 DE priority documents to show that the claims of PCT/DE03/03988 are supported by these priority documents. Applicant should note that the support provided by these priority documents must be for the full scope of the claims, including all of the Markush group members of any rejected claim that are not shown by the cited reference. See the fact situation of In re Ruscetta 255 F.2d 687, 118 USPQ 101.

In the event that applicant can show that these priority documents support the claims of PCT/DE03/03988, then the claims are rejected under 35 U.S.C. 102(a), since the reference has authors who are not inventors. To overcome, applicant may file a Rule 1.132 declaration in accord with In re Katz 687 F.2d 450, 215 USPQ 14.

Wallukat et al (2002) show an ELISA immunoassay that detects autoantibodies present in a patient's bodily fluid. An ammonium sulfate precipitate of the bodily fluid sample is prepared. The resolubilized autoantibodies therefrom are then contacted with a biotinylated peptide having a sequence derived from the second loop of the human Angeotensin II AT1 receptor. The thus contacted sample is then contacted with Streptavidin coated magnetic beads; the autoantibodies bound thereto are then detected with enzyme labeled anti-human IgG3 antibodies. The presence of IgG3

autoantibodies is indicative of preeclampsia. As such, instant claims 1-5 and 7-10 are anticipated.

Regarding claim 15, any peptide having a sequence derived from the second loop of the human Angeotensin II AT1 receptor would inherently involve "deletions" – i.e. deletions of receptor residues that flank the loop peptide.

Regarding claim 37, any peptide having a sequence derived from the second loop of the human Angeotensin II AT1 receptor would inherently be a "partial sequence" of the loop, since there would be a deletion of flanking residues.

NEW REJECTION(S) UNDER 35 USC 103

Claims 12, 32 And 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallukat et al al (In vitro Cellular, vol. 38, 376-377, Jul/Aug 2002) in view of Wallukat et al (WO 00/39154, cited in IDS of 1/27/09).

Wallukat et al (2002) do not disclose the sequence of the peptide having a sequence derived from the second loop of the human Angeotensin II AT1 receptor that was used in their ELISA. Wallukat et al (WO 00/39154) disclose the sequences of peptides that are derived from the second loop of the human Angeotensin II AT1 receptor and that bind to pathological autoantibodies that are involved in preeclampsia. The Office finds that peptides having instant SEQ ID NOS:9 and 10 are disclosed. Thus instant dependent claim 12 would have been obvious.

Independent claims 32 and 35 are rejected because they recite no particular steps involved in "detecting" the autoantibodies. Most certainly then, the immunoassay steps shown by Wallukat et al (2002) are within the scope of these claims.

CONTACTS

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, whose telephone number is 571-272-0849. The examiner can normally be reached on Mon.-Thu. from 8:00 am to 5:30

pm and on alternate Fridays. The fax phone number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Typed 4/10/09 DAS

/David A Saunders/

Primary Examiner, Art Unit 1644